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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Docket Number 00N-1380**
**Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction Repair (FDA Public Meeting August 2, 2000)**

Dear Sir or Madam:

This letter comments on the critical issues raised in the above-referenced public meeting involving the Food and Drug Administration's (FDA) regulation of human bone allograft.

We strongly urge FDA to remove the "homologous use" and "minimal manipulation" criteria from the proposed rules governing tissue-based products. FDA received an overwhelming number of comments opposed to the application of the criteria to human bone allograft (See FDA Dockets 97N-484R and 97N-484S)[1].

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In addition, most speakers at the public meeting, representing a variety of interests (from orthopedic and neurological surgeons to patients, donor families and industry representatives) made clear that the proposed criteria's application to bone allograft used for spinal/orthopedic repair or restoration are impractical in application, clinically illogical, and most likely do not benefit patient health.

Because the "minimal manipulation" and "homologous use" criteria are crucial to determining which pre-shaped bone allograft would be "kicked-up" and regulated as a medical device pursuant to § 351 of the Federal Food, Drug and Cosmetic Act (FFDCA), or remain regulated as a tissue product under § 361 of the Public Health Service Act (PHSA), it is very important that the criteria fairly, clearly and accurately describe product that would be regulated as a medical device. Accordingly, the proposed "minimal manipulation" and "homologous use" criteria should be removed or, alternatively, amended to *clearly* identify which products will be regulated as devices or tissue.

Below we address FDA's posed questions and make additional comments:

**1. Which processing procedures applied to human bone allograft fall within, or outside of, FDA's proposed definition for "minimal manipulation?"**

Before we comment on which products fall within the proposed definition, it is important to note that the "minimal manipulation" definition is flawed. As proposed, "minimal

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[1] "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products." 63 Fed. Reg. 26744 (May 14, 1998) (FDA Docket No. 97N-484R) and "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." 64 Fed. Reg. 52696 (Sept. 30, 1999) (FDA Docket No. 97N-484S).

manipulation" is defined as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement." See 64 Fed. Reg. 52696, 52700. Seizing on a few key words in this definition, a majority of the speakers at the public meeting explained that human bone allograft used in orthopedic repair always maintains the relevant characteristics of bone tissue -- i.e., restoration of structural support -- no matter the amount of manipulation.

A number of public speakers criticized the proposed "minimal manipulation" criterion by explaining that the manipulation to pre-shaped bone allograft does not alter the relevant characteristics of bone tissue. For example, Dr. Scott Kitchel, an orthopedic spine surgeon from the University of Oregon explained that "manipulating bone to form threaded cortical bone dowels does not alter the original relevant characteristics of bone and to me, minimal manipulation allows that I change bone [for use in the spine, etc.] whether I do that freehand in the operating room or it is given to me in a more precise manner . . . the manipulation [does not] alter the relevant characteristics of that bone, which to me are structural support and allowing bone to grow through it." (Transcript (T) at 71-72).

Dr. Richard Fessler, on behalf of the American Association of Neurological Surgeons, stated that "preshaping the bone does not alter its relevant characteristics or its utility for reconstruction, repair and replacement . . . The definition is not clinically relevant." (T. 116).

The AATB further criticized the definition, stating "all criteria should be predictable and easily understood by anyone covered by the regulation. This is not the case with the proposed criterion for minimal manipulation. We anticipate that this criterion could be very difficult to apply in a consistent and unbiased manner." (T. 127).

As for applying the proposed definition--i.e., FDA's first question regarding the proposed criterion's application to products---pre-shaped bone allograft clearly falls within FDA's proposed definition of "minimally manipulated." In FDA's first proposed rule governing registration and listing, FDA identified certain procedures that would be considered minimal manipulation, such as: cutting, grinding, shaping, soaking in antibiotic solution, sterilization by ethylene oxide treatment or irradiation, cell separation, lyophilization; cryopreservation; and freezing. 63 Fed. Reg. 26744, 26748 (emphasis added).

Pre-shaped bone allograft, whether smooth or threaded or from long or short bone, is produced by cutting, shaping, grinding, and or freezing bone. The AATB described the variety of techniques that are used to form bone allograft products such as "cutting, sawing, grinding, milling, drilling, lathing and other similar activities are performed to ready the graft for the use as requested directly or indirectly by the surgeons." (T. 48). All of these techniques fall within the proposed definition for minimal manipulation. More important, following these cuttings, grindings and different forms of shaping, the bone allograft retains its relevant reconstructive characteristics and, therefore, meets FDA's proposed definition for minimal manipulation.

Finally, FDA should acknowledge that the amount of manipulation used in processing preshaped bone allograft for orthopedic/spinal reconstruction and repair should be considered minimal. As FDA stated previously, "[it] recognizes that the subsequent accumulation of clinical data and experience about a particular process may demonstrate that it does not alter the original relevant characteristics of the . . . tissue, and the agency will consider this information in determining whether a procedure should be considered minimal as opposed to more-than-minimal manipulation." 63 Fed. Reg. 26744, 26748-49. After the extensive presentation of data and clinical experience at the public meeting regarding bone allograft's utility for reconstruction, replacement and repair--that is not altered by the processing of the tissue--FDA should formally and clearly state that all bone allograft not combined with drugs or man-made devices meets the "minimal manipulation" criterion.

**2. Which uses of human bone allograft fall within, or outside of, FDA's proposed definition for "homologous use?"**

Again, before we comment on the proposed definition's application to certain product, we first address the problems with the proposed "homologous use" criterion. "Homologous use" is defined as "the use of a . . . tissue based product for replacement or supplementation and . . . [f]or structural tissue based products . . . when the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs." 64 Fed. Reg. 52696, 52700.

Utilizing bone allograft from the fibula or other part of the body in spinal and/or orthopedic surgery is always used in a homologous manner because bone replacement and restoration of structure is the purpose of the surgery. With regard to bone used in spinal fusion, the use of the allograft will always be homologous because the bone allograft is replacing bone, even if the bone is placed in the disc space, the bone is there to fuse with other bone. As one doctor described it, "you are not trying to replace a disc, you are trying to fuse two bony segments." (T. 44).

The problem with the proposed "homologous use" criterion is exemplified by Dr. Ruth Solomon's opening remarks regarding her interpretation of "homologous use." She stated that connecting two vertebrae in a spinal fusion would not be considered homologous because the space between the vertebrae is not a place where bone is traditionally located. Dr. Solomon later clarified her remarks at the public meeting by stating homologous means "bone-to-bone. It doesn't have to be the same bone, but bone from a donor going into a location in the recipient where bone normally is found is what we had in mind by that." (T. 44)

Dr. Solomon's interpretation of the "homologous use" definition sparked numerous comments and criticisms. Dr. Heany for the AANS explained that "uniformly in spine surgery, every time we use allografts as a neurosurgeon, we are connecting two pieces of bone, one above to one below, spanning a place where at least a single intervertebral disk was located." (T. 60)

Dr. Kitchel stated that "bone is really used for grafting or to make bone grow to other bone. Bone isn't used as a joint replacement, bone is really put where you want bone to grow, so it is bone being put in a position for bone." (T. 68-69) "There are only two real kinds of bone . . . and it doesn't matter whether that comes from the femur or the tibia or the spine or the skull or any other bone in the body." (T. 69) Dr. Richard Fessler from the AANS stated, "using bone to fuse bone to bone is homologous use." (T. 114)

The AATB explained that the proposed "homologous use" criterion is based on a misperception that ignores current standards of surgical practice in tissue banking and implies that if a tissue is transplanted for the same use and in the same or analogous anatomical site from which it was recovered, then, its use is somehow more basic and less risky to patients. (T. 124). AATB further explained that:

> "Bone grafts intended for use in interbody spinal fusion are among the most common applications of grafting in orthopedics and neurosurgery. The FDA's homologous use criterion could lead to the conclusion that bone grafts do not fit within the definition of tissues because the joint space between the vertebrae is normally filled with a fibrocartilaginous disc, and not a bony tissue. The conclusion could result in disruption of the well-established surgical practice of spinal fusion for which the attendant risk of bone grafting are well understood."

The bottom line is that cancellous or cortical bone taken from any part of the body is indistinguishable from cancellous or cortical bone taken from any other part of the body, and the imposition of an artificial location definition for homologous use "doesn't make clinical sense." (T. 168)

While the proposed criterion specifies that in determining whether a product is homologous or non-homologous, FDA will focus on how the product is labeled or promoted by the manufacturer as opposed to the intended or actual use of the product by practitioners, this does not solve the problem with the proposed definition in the first instance. If the definition for "homologous use" does not make sense to begin with, then the "labeling" requirement does nothing to clarify or redeem the ultimate effect of the proposed criterion.

If, however, FDA retains the "homologous use" criterion, then FDA should make clear that bone allograft used in spinal surgeries, is homologous use, no matter the location of the initial bone. For example, FDA's previous examples of homologous use claims include "bone allograft obtained from a long bone but labeled for use in a vertebra." 63 Fed. Reg. 26754, 26749. Based on this statement, it appears that FDA, at one point, considered bone dowels to be homologous, and yet, at the public meeting convened last year, FDA announced that it intended to classify bone dowels as medical devices. This schizophrenic regulatory treatment of tissue products provides a perfect example for what is wrong with the proposal. Therefore, FDA should eliminate the homologous use criteria or in the alternative, follow its previous interpretation of homologous as set forth in the first proposed registration rule.

**3. What risks to health have been identified and characterized for human bone allograft products?**

The risks to human bone allograft cannot be analyzed in a vacuum. As Dr. Heary from the AANS described, there are basically three choices surgeons may use for structural support in spine surgery: "what we can put in the space to maintain the structural support would either be autograft bone coming from either the patient's illiac crest or their own fibula . . . allograft bone available from the tissue bank, or metal instrumentation, which may be made of either steel or titanium." (T. 63). By comparing pre-shaped bone allograft to surgically prepared allograft, autograft bone and other products made from metal, we can better analyze the relative risks associated with bone allograft.

First, pre-shaped bone allograft bone is recognized as easier to use and less likely to become dislodged from the surgical site than bone (either allograft or autograft) shaped by the surgeon at the time of surgery. Further, autograft bone or the interoperative preparation of allograft implants, will increase the operative time, increase the likelihood of infection and donor site morbidity, increase patient blood loss and, with autograft bone, be of limited supply. For all these reason, as numerous surgeons explained, the pre-shaped allograft is simply a better alternative to autograft or surgically-shaped allograft and allows for a potential improved patient outcome. In fact, Dr. Sandu from Cornell University, explained that the "availability of precision pre-cut allografts has markedly reduced the risks associated with anterior spinal fusion surgery." (T. 195). Thus, for the sake of the public health, the offering of precise preshaped allograft implants processed under sterile conditions and in accordance with FDA donor

screening and testing requirements and voluntary standards promulgated by the AATB---should be encouraged by the FDA rather than discouraged.

In addition, processed bone allograft has minimal risks of disease transmission and a high surgical success rate. Dr. Heary from the AANS explained that unprocessed bone has a very minimal risk of disease, and "processed bone has essentially no risk of disease transmission." (T. 64). The use of allograft bone has been the subject of numerous articles, many of which demonstrate that allograft is used very successfully, with approximately 90 - 95% success rates. (T. 112).

Finally, bone allograft is recognized as superior to metallic devices because of the benefits of the bone properties. Dr. Sandu stated: [m]y colleagues and I believe that structural allografts are far superior to the widely used metallic interbody fusion devices both mechanically and biologically. From a mechanical standpoint, the compressive strength of cortical allografts generally exceed physiologic loads. . . bone allograft materials are biologically superior to metallic device products because of their capacity to incorporate to host bone, to remodel according to physiologic loads, and to ultimately resorb." (T. 196).

**4. What controls have been identified to adequately address the risk to health of human bone allograft products?**

There are a number of controls that address the risk to health of human bone allograft. First, FDA's donor screening and testing requirements, set forth in 21 C.F.R. pt 1270, provide

requirements for recovery, screening, testing, processing, storage and distribution of human tissue. Individual states also have requirements governing the recovery, processing, storage and distribution of human tissue. Finally, most tissue banks follow the AATB's voluntary standards for tissue banking, which establish performance requirements for donor selection as well as for the storage, processing, and distribution of tissue.

**5. What industry standards for bone allograft products are available, and what standards will be needed in the future?**

Again, the AATB standards are available to address what FDA has traditionally regarded as the most critical issues raised by transplantable tissue---disease transmission and contamination. Moreover, any additional concerns regarding preparation of human bone could be addressed in FDA's good tissue practice regulations, which should be published sometime this fall.

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For the reasons set forth above, we strongly recommend that FDA remove the proposed "homologous use" and "minimal manipulation" criteria from its proposed regulatory framework for regulating tissue products.

Sincerely,

Ed Basile /AW

Edward M. Basile

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